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Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003

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Since January 1995, all European Union applications for marketing approval for medicinal products derived from biotechnology and other drugs considered potentially innovative follow the EMEA centralized procedure. In order to assess the overall degree of therapeutic innovation of these drugs, we considered, for each approved agent, its target, the availability of previous treatments and the extent of its therapeutic effect. The following scores for therapeutic innovation were assigned through a consensus process: 'A' (important), 'B' (moderate) and 'C' (modest). The overall degree of important/moderate therapeutic innovation was 47% of all therapeutic agents (32% important; 15% moderate). Most (80%) of the EMEA-approved therapeutic agents were for serious diseases. The remaining ones were for risk factors (7%) or nonserious diseases (13%).

Introduction

In January 1995, the European Medicines Evaluation Agency (EMEA) was established. Since then, all applications for marketing approval for medicinal products for human and veterinary use derived from biotechnology are required to follow the centralized procedure. In addition, other nonbiotechnological drugs, if considered potentially innovative, may access, at the discretion of the applicant, either this procedure or the European mutual recognition procedure starting from a national drug agency.

The degree of innovation achieved by newly approved agents is a matter of debate [1–3]. According to the International Society of Drugs Bulletins' declaration [4], the concept of 'therapeutic' innovation indicates a new treatment that entails benefits to the patient when compared with previously existing options. On the other hand, drugs that simply provide better kinetics, improved compliance, or have a new mechanism of action without showing an improved therapeutic outcome can be classified as 'pharmacological' innovation; likewise, a 'technological' innovation is represented by already available drugs obtained via biotechnology, or those based on a new delivery system.

This paper aims to assess the overall degree of therapeutic innovation by a retrospective analysis of all active substances for human use approved by the EMEA between 1995 and 2003.

Methods

The list of drugs approved by the EMEA (January 1995 through the first 6 months of 2003) was downloaded from the European Drug Regulatory Authorities (EUDRA) website: http://pharmacos.eudra.org/F2/register/register.htm. Different medicinal products were considered as a single entity when active substance, Anatomical Therapeutic Chemical (ATC) code and therapeutic indication were the same. Information on approved drugs was collected from several documents, including the European Public Assessment Reports [5], and from scientific literature searches using PubMed.

The first step was to divide the approved agents into six classes according to their targets as designated by their approved indication: therapeutic agents for (a) serious diseases (a disease is serious if it meets one of the following criteria: it is fatal, it requires hospitalization, it is life-threatening or heavily disabling: this definition is based on the similar definition of a serious adverse drug reaction and on the EMEA document CPMP/495/96 rev. 1); (b) risk factors for serious diseases (e.g. hypertension or obesity); (c) nonserious diseases (e.g. allergic rhinitis); (d) diagnostics; (e) life-style drugs [6]; (f) vaccines. The last three classes were not further considered for the analysis on therapeutic innovation (strictly speaking, the agents included therein were not therapeutic). However, we felt that it was important to analyse therapeutic innovation in classes a–c separately, because the public health impact of an important therapeutic innovation may differ for each class.

For each therapeutic agent of classes a, b and c, the degree of therapeutic innovation was assessed by evaluating (1) the availability of previous treatments, and (2) the extent of the therapeutic effect. For both (1) and (2), we assigned A, B or C scores (in decreasing order of importance) as indicated in Figure 1.

The scores for availability of previous treatments were: A = drugs for diseases without recognized standard treatment at the time of their approval (e.g. imiglucerase, agalsidase, riluzole); B = drugs for diseases where subsets of patients are less responsive to marketed drugs and/or other medical interventions (e.g. infliximab, imatinib), and C = drugs for diseases responsive to marketed drugs or other medical interventions (e.g. antihypertensives, insulin). Class C drugs were further divided into C_1 (more effective or safer than existing drugs), C_2 (mere pharmacological innovation, i.e. drugs with better kinetics or new mechanism of action), and C_3 (mere technological innovation, i.e. a new chemical or biotechnological product with therapeutic role similar to already existing ones).

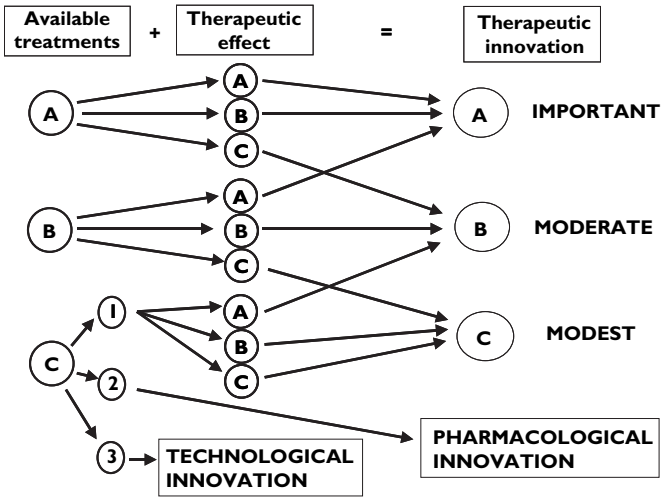

Figure 1
Algorithm used to assign the overall score for innovation. **Available treatments:** A = drugs for diseases without recognized standard treatment; B = drugs for diseases where subsets of patients are less responsive to marketed drugs and/or other medical interventions, C = drugs for diseases responsive to marketed drugs or other medical interventions (C_1 = more effective or safer than existing drugs; C_2 = mere pharmacological innovation, i.e. drugs with better kinetics or new mechanism of action; C_3 = mere technological innovation, i.e. a new chemical or biotechnological product with therapeutic role similar to already existing ones). **Therapeutic effect:** A = major benefit on clinical end-points (e.g. increased survival rate and/or quality of life) or validated surrogate end-points; B = partial benefit on the disease (on clinical or validated surrogate end-points) or limited evidence of a major benefit (inconsistent results); C = minor or temporary benefit on some aspects of the disease (e.g. only partial symptomatic relief of a serious disease).

The therapeutic effect scores were: 'A' = major benefit on clinical end-points (e.g. increased survival rate and/or quality of life) or validated surrogate end-points [7]; 'B' = partial benefit on the disease (on clinical or validated surrogate end-points) *or* limited evidence of a major benefit (inconsistent results); and 'C' = minor or temporary benefit on some aspects of the disease (e.g. only partial symptomatic relief of a serious disease).

Overall scores for therapeutic innovation ('A', important; 'B', moderate; 'C', modest) were assigned according to the algorithm detailed in Figure 1, which shows that the overall extent of therapeutic innovation depends primarily on treatment availability and on the effectiveness of the new therapy. Three authors (DM, FDP and

NMo) independently assigned scores to each drug. In case of disagreement, the final scores were assigned through a consensus process (by discussion). All authors unanimously approved the final scores.

Results

From 1995 through the first 6 months of 2003, the EMEA approved 235 medicinal products, corresponding to 177 active substances: 151 therapeutic agents, 12 diagnostics, one life-style drug and seven vaccines. For six products, marketing authorization was subsequently voluntarily withdrawn for commercial reasons by the applicants (these were excluded from further analysis, and in any case their exclusion did not change the final results, because two were vaccines and three contained active substances still available in other EMEA-approved products).

Among the 151 therapeutic agents (Table 1), 36% were biotechnological products and 80% were for serious diseases. Overall, 71 agents (47%) represented important/moderate therapeutic innovation (32% important; 15% moderate).

Among the 121 active substances for serious diseases, 38.8% represented important therapeutic innovation (e.g. carglumic acid, scored 'A' (available treatments) + A (therapeutic effect) = A; infliximab, imatinib, HIV protease inhibitors, enfuvirtide, all scored B + A = A), 15.7% were considered moderate therapeutic innovation (e.g. rivastigmine and riluzole, both scored A + C = B and entacapone, scored B + B = B) and 3.3% were modest therapeutic innovation (e.g. alitretinoin and temozolomide, both scored B + C = C). The remaining 51 active substances (42%) represented pharmacological (e.g. glitazones, repaglinide, telithromycin) or technological innovation (e.g. recombinant human insulin, recombinant coagulation factors, recombinant somatotropin), or both (insulin glargine and insulin lispro).

Among the 30 drugs approved for risk factors or nonserious diseases, 83% represented merely pharmacological or technological innovation (e.g. desloratadine, scored C3 + A, i.e. technological innovation, and several antihypertensives, e.g. telmisartan, scored C2 + A, i.e. pharmacological innovation) and only 17% were important/moderate therapeutic innovation (e.g. sildenafil, scored A + A = A (important) and raloxifene, scored C1 + A = B (moderate)).

Discussion

In the period under scrutiny, most (80%) of the EMEA-approved therapeutic agents were indicated for the treatment of serious diseases. Although the overall degree of important/moderate therapeutic innovation reached 47%, nontherapeutic innovation prevailed among drugs targeted to risk factors or nonserious diseases. It should be noticed that the possible bias towards innovative drugs (the applicant may choose whether or not to sub-

Table 1
EMEA-approved therapeutic agents according to the degree of innovation

	Agents for serious diseases			Agents for risk factors for serious diseases			Agents for nonserious diseases			Overall	
Degree of innovation	*n* (*)	%†	% of biotechnological agents (out of 121)	*n* (*)	%‡	% of biotechnological agents (out of 11)	*n* (*)	%§	% of biotechnological agents (out of 19)	*n*	%
A	47 (14)	38.8	11.6	0	0	0	2	10.5	0	49	32.5
B	19 (5)	15.7	4.1	2 (0)	18.2	0	1	5.3	0	22	14.6
C	4 (1)	3.3	0.8	0	0	0	0	0	0	4	2.6
Pharm	28 (13)	23.1	10.7	9 (2)	81.8	18.2	7 (1)	36.8	5.3	44	29.1
Tech	23 (16)	19.0	13.2	0	0	0	9 (3)	47.4	15.8	32	21.2
Total 151 (55)	121 (49)	100	40.4	11 (2)	100	18.2	19 (4)	100	21.1	151	100

*A = important, B = moderate, C = modest, Pharm = pharmacological innovation, Tech = technological innovation.*in parentheses, the number of therapeutic agents derived from biotechnology; †% with respect to the total number of agents for serious diseases (n = 121); ‡% with respect to the total number of agents for risk factors for serious diseases (n = 11); §% with respect to the total number of agents for nonserious diseases (n = 19).*

mit the dossier through the centralized procedure) is, in our opinion, counterbalanced by the significant number of merely biotechnological products (e.g. new formulations of recombinant human hormones), which are compulsorily submitted through this procedure (55 out of 151 therapeutic agents).

The scores assigned to some therapeutic agents deserve some comments. For instance, HIV protease inhibitors received marketing authorization when several other antiretroviral drugs were already available. Nevertheless, there is consensus in the literature that, in the case of HIV infection, the availability of several drugs is important to address the problem of drug resistance [8]. Therefore, the final score for therapeutic innovation was 'A' (important), resulting from scores 'B' (available treatments) and 'A' (therapeutic effect). In contrast, the introduction of antihypertensive agents such as new angiotensin II receptor antagonists is considered a mere pharmacological innovation in our algorithm.

Another interesting example is provided by rivastigmine and riluzole (indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis): although both drugs scored 'A' for available treatments, their modest therapeutic effect ('C') led to a final score 'B' for therapeutic innovation. Likewise, entacapone received a final score 'B', resulting from a score 'B' for available treatments and a score 'B' for therapeutic effect.

Finally, among drugs for nonserious diseases, sildenafil, tadalafil and vardenafil provide a good example. All drugs were considered to provide major benefit (score 'A' for therapeutic effect), but only sildenafil was considered an important therapeutic innovation because when it was approved in 1998 it radically changed the treatment of erectile dysfunction (score 'A' for available treatments). In contrast, tadalafil and vardenafil were approved in 2002 and 2003, respectively. Hence, they scored only 'C2' for available treatments and were classified as pharmacological innovations.

We are aware that data of relative efficacy are often difficult to assess and, in most cases, are unavailable at the time of marketing authorization. To carry out our analysis, we used an official source of information (European Public Assessment Reports) and the published literature. This is one limitation of the study and it is possible that scores for therapeutic innovation may change as new evidence becomes available (approved indications of a given agent may also change over time). For these reasons, we think that the full list of the scores for therapeutic innovation, as assigned by us to EMEA-approved active substances for this analysis, should be publicly offered to comments and criticisms (see http://www.crevif.it and follow the link to therapeutic innovation).

In conclusion, because therapeutic innovation is frequently and controversially debated in the literature, we have tried to address this question quantitatively by developing an algorithm that is proposed to the scientific community for further improvement. Using this algorithm, less than 50% of the EMEA-approved therapeutic agents represented important/moderate therapeutic innovation. Biotechnological or pharmacological innovation (23% and 19%, respectively, among agents for serious diseases) should not be confused with therapeutic innovation, because only the latter is an important public health goal.

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Conflict of interest: All authors declare that they have no conflict of interest.

Dr Pasqualino Rossi is member of the Committee for Proprietary Medicinal Products (CPMP) at the EMEA. Dr Nello Martini is the Director General of the Italian Medicines Agency. The opinions expressed herein are those of the authors and do not necessarily reflect the views of the European Medicines Evaluation Agency or the Italian Medicines Agency.

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